

MEDICAL AFFAIRS



Current SCD therapies and the role of Automated RBC Exchange: A review of recent literature & guidelines.

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MEDICAL AFFAIRS, TERUMO BCT

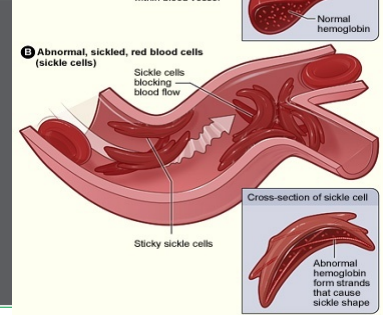
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Presentation overview:

- Review of current therapies in management of SCD complications
- Update on recent ASFA 2016 guidelines for RBCx and NICE Guidance.

Sickle Cell Disease: Complications



Many SCD complications (acute chest syndrome & stroke,) are due to the obstruction of small vessels by the abnormally shaped RBCs. There are also evidence of:

1. Platelet & Endothelial Cell Activation
 2. Increased Thrombin Generation
 3. Increased levels of Tissue Factor
 4. Increased plasma markers of coagulation
 5. SS RBC adhesion to activated Endothelial Cells
 6. Activation markers that correlate with RBC hemolysis
- Lack of tissue oxygenation (ischemia) can cause painful crises, damage to body organs and even death
 - Elevated HbS levels correlate with increased blood viscosity,¹ which can decrease blood flow and oxygen transport
 - Other complications (anemia) have to do with the premature destruction of the abnormal RBCs in the spleen
 - All the above mentioned complications among others, impose a disease burden and challenges that impact the patients, their families, & the Health Care Providers.

1. Hilliard L, et al., "Erythrocytapheresis Limits Iron Accumulation in Chronically Transfused SCD Patients." *Am J Hematol* 1998; 59: 28-35.

Social & Economic Burden of SCD

- During 2005, medical expenditures for children with SCD averaged \$11,702 for children with Medicaid coverage and \$14,772 for children with employer-sponsored insurance. About 40% of both groups had at least one hospital stay
- An average of 75,000 hospitalizations per year due to SCD occur in the United States, costing approximately \$475 million.

Children and Sickle Cell Disease: Annual Average Medical Expenses by Type of Insurance*						
	Medicaid			Private Insurance		
	Children with SCD	Children without SCD	Costs due to SCD	Children with SCD	Children without SCD	Costs due to SCD
Inpatient admissions	\$5,963	\$359	\$5,604	\$7,820	\$229	\$7,591
Outpatient visits	\$4,063	\$349	\$3,714	\$6,371	\$829	\$5,582
Prescription drugs	\$1,049	\$317	\$732	\$531	\$235	\$296
Total expenses	\$11,075	\$1,706	\$9,369	\$14,722	\$1,293	\$13,469

*All expenses are average per child

Sickle Cell Disease: Patient Treatment Options

- **Hydroxyurea**
 - Stimulates the production of hemoglobin F (HbF). By 5-15 %.
 - HbF inhibits the sickling of RBCs containing HbS naturally in the fetus and infants
- **Transfusion Therapy** (*iron chelation therapy may be required*)
 - Simple transfusion: infusion of normal RBCs (HbA), without removal of HbS
 - Red Blood Cell Exchange (erythrocytapheresis): removes “defective” RBCs while infusing healthy RBCs
 - Automated – “simultaneous” removal and infusion of RBCs
 - Manual – “sequential” removal and infusion of RBCs
- **Stem cell transplantation**
 - Only known potential cure for sickle cell disease¹

1. Krishnamurti L, et al., “Stable Long-Term Donor Engraftment following Reduced-Intensity Hematopoietic Cell Transplantation for Sickle Cell Disease.” *Blood Marrow Transplant* 2008; 14: 1270-1278.

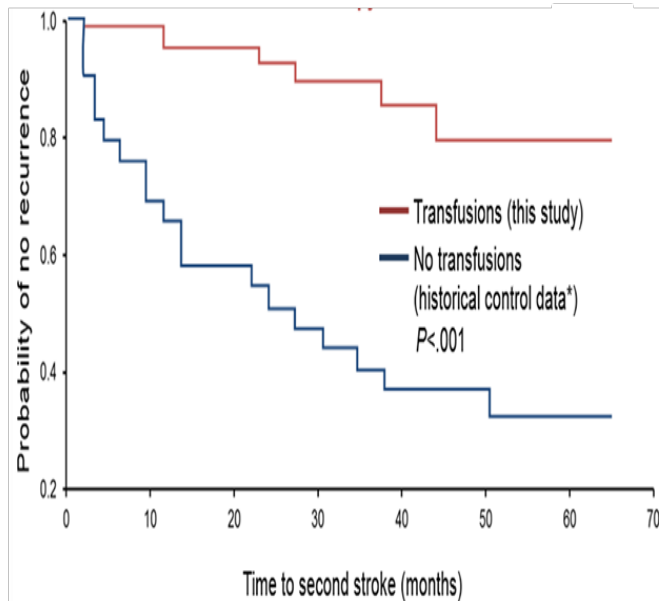
Therapy Goals for Transfusion Therapy

- Common goal of transfusion therapy and exchange transfusion is to decrease the level of hemoglobin S to less than 30% of the total hemoglobin^{1,2,3,4}
- Other goals include:^{5,6}
 - Improve oxygen carrying capacity by increasing amount of hemoglobin A
 - Decrease blood viscosity and increase oxygen saturation by decreasing percent HbS
 - Suppress production of RBCs containing HbS by increasing tissue oxygenation

1. Cabibbo S, et al., "Chronic RBC Exchange to Prevent Clinical Complications in Sickle Cell Disease." *Transfus Apher Sci* 2005; 32: 315-321.
2. Adams D, et al., "Erythrocytapheresis Can Reduce Iron Overload and Prevent the Need for Chelation Therapy in Chronically Transfused Pediatric Patients." *J Pediatr Hematol Oncol* 1996; 18 (1): 46-50.
3. Kozanoglu I, et al., "Automated Red Cell Exchange Procedures in Patients with SCD." *Transfus Apher Sci* 2007; 36: 305-312.
4. Vichinsky EP, et al., "Causes and Outcomes of the Acute Chest Syndrome in Sickle Cell Disease." *N Engl J Med*; 2000;342:1855-1865.
5. Swerdlow PS, "Red Cell Exchange in Sickle Cell Disease." *American Society of Hematology*, 2006 pp, 48 - 53.
6. Danielson C, et al., "The Role of Red Blood Cell Exchange Transfusion in the Treatment and Prevention of Complications of Sickle Cell Disease." *Ther Apher*, 2002; 6 (1): 24-31.

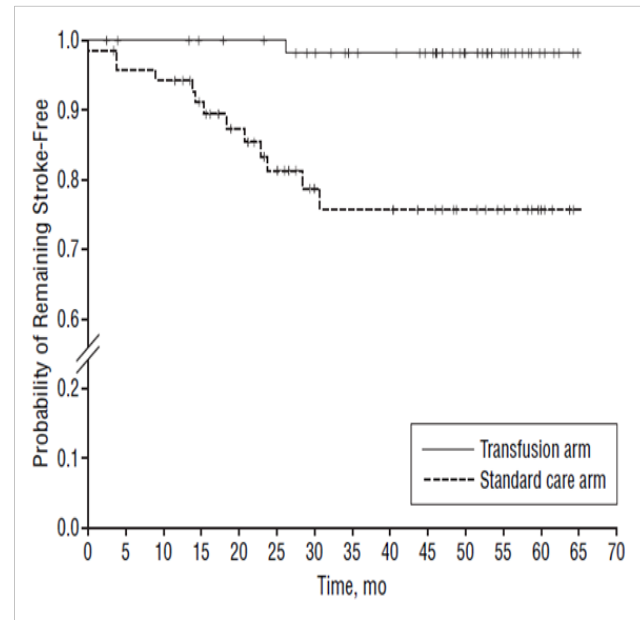
Chronic Transfusion Therapy for SCD

Secondary Stroke Prevention



Retrospective review
60 patients on chronic transfusions
8 centers
 Pegelow CH, et al. J. Pediatr: 1995

Primary Stroke Prevention



STOP Trial
 Adams RJ, et al. NEJM: 1998

Complications of Transfusion

Iron overload

Allo / autoantibody formation

Delayed Hemolytic Transfusion Reactions

Transfusion reactions (allergic, febrile)

Transfusion-transmitted infections

CVL thrombosis/infection

Immune dysregulation

Others yet to be identified

Impact of Iron Overload

Growth Failure

Pubertal Delay

Diabetes

Heart/Liver Failure

Hypothyroid



Birth 5 yr 10 yr 15 yr 20 yr 25 yr 30 yr

1995

1998

2015

Pegelow
CH, et al.
12

Adams RJ, et al.
(STOP)

Today

Benefits of ARBCX versus Manual Exchange Transfusion and Simple Transfusion (“Top Up”)

Automated RBCX provides the following advantages over simple transfusion and manual exchange:

- rapidly removes RBCs containing hemoglobin S and replaces them with normal (HbA) RBCs^{1,2,3,4,5}
- manages iron overload and blood viscosity^{1,4,9}
- allows for precise control of hemoglobin S and hematocrit^{3,4,6,7,8}
- maintains isovolemia^{3,4,9}

1. Adams D, et al., “Erythrocytapheresis can reduce iron overload and prevent the need for chelation therapy in chronically transfused pediatric patients.” *J Pediatr Hematol Oncol* 1996; 18 (1): 46-50.
2. Danielson C, et al., “The role of Red Blood Cell Exchange transfusion in the treatment and prevention of complications of sickle cell disease.” *Ther Apher*, 2002; 6 (1) : 24-31.
3. Wahl S, et al., Lower alloimmunization rates in pediatric sickle cell patients on chronic erythrocytapheresis compared to chronic simple transfusions.” *Transfusion* 2012; 52:2671-2676.
4. Lawson, et al., “Red cell exchange in sickle cell disease.” *Clin. Lab. Haem.*1999; 21: 99–102.
5. Wayne, S, et al., “Transfusion Management of Sickle Cell Disease” *Blood* 1993; 81: 1109 -1123.
6. Cabibbo S, et al., “Chronic RBC exchange to prevent clinical complications in sickle cell disease.” *Transfus Apher Sci* 2005; 32: 315-321.
7. Hilliard L, et al., “Erythrocytapheresis limits iron accumulation in chronically transfused SCD patients.” *Am J Hematol* 1998; 59: 28-35.
8. Duclos C, et al., “Long-term red blood cell exchange in children with sickle cell disease: Manual or automatic?” *Transfus Apher Sci* 2013; 219–222 .
9. Singer S, et al., “Erythrocytapheresis for chronically transfused children with sickle cell disease: An effective method for maintaining a low HbS level and reducing iron overload.” *J Clinical Apher* 1999; 14:122-125.

Other possible benefits of Automated Red Blood Cell Exchange

- RBCx also rapidly decreases the rate of haemolysis which can decrease liver processing of bilirubin, damage to renal tubular cells and the scavenging of nitric oxide by free hemoglobin released from sickle cells.
- The beneficial effects on blood viscosity, elasticity, and relaxation time, and reduction of adhesion molecule level like sVCAM-1 has been documented after RBC exchange
- Reduces Circulating Endothelial Cells (CEC)
- Control of patients Hct % & HbS
- Possible social benefits: patients ownership of the disease & improved quality of life.

Main points: RBCX vs ST

- *Retrospective (n=45): 23 patients on ST and 22 on RBCX*
- *benefits: isovolemic, lower hyperviscosity, more effective in lowering HbS, limits iron overload*
- *Stroke patients preferentially on RBCX to prevent future iron overload and to better control percent HbS*

With limited phenotype matching RBCX lower alloimmunization rates vs ST:

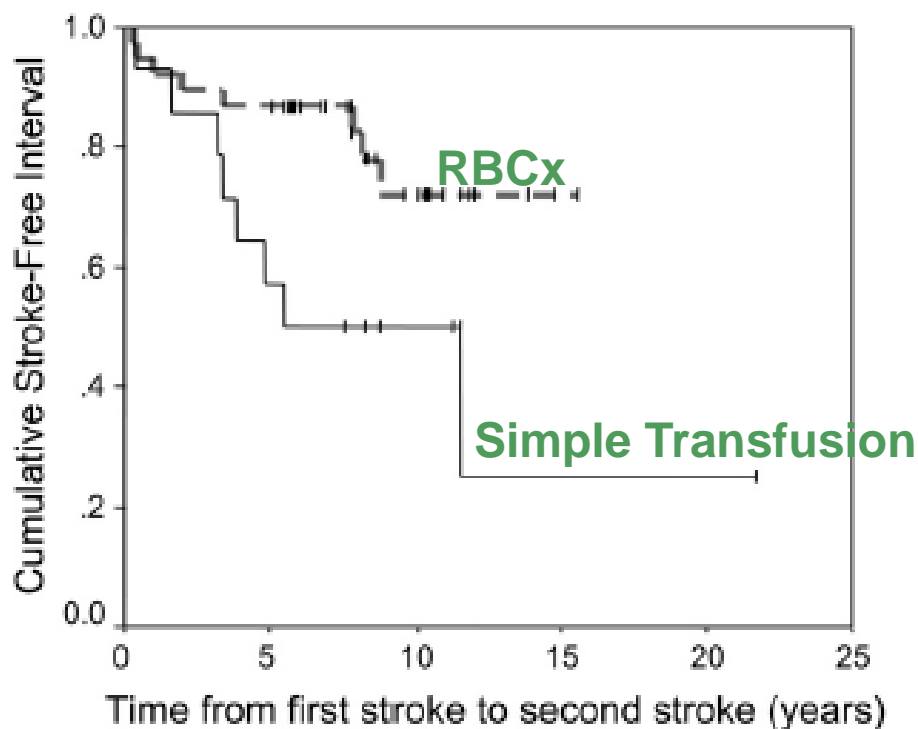
- *The ARBCX group received significantly more blood & 3 patients developed antibodies, while 4 patients developed antibodies in the ST group.*
- *mechanism not known*
- *alloimmunization concerns may be unjustified*

Limitations:

- *reporting of patient reactions was voluntary (underreported)*
- *inconsistencies on number of RBCX versus ST procedures from patient to patient*
- *further prospective trials are needed*

Simple Transfusion vs. RBCx in Stroke prevention

- A retrospective cohort study of 137 children with SCD and strokes compared RBCx and Simple Transfusion in their ability to prevent the occurrence of a second stroke
- Children receiving simple transfusion had a **5-fold greater relative risk** of second stroke than those receiving RBCx



Sergio Cabibbo *, Carmelo Fidone, Giovanni Garozzo, Agostino Antolino, Giovanna Oriella Manenti, Francesco Bennardello, Vincenzo Licitra, Salvatore Calabrese, Francesco Costantino, Simone Travali, Roberto Distefano, Pietro Bonomo

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- Retrospective (1999-2004): tracked for an average of 6 years a 394 (manual & automated =206) procedures (CS3000, MCS+ & COBE) exchanges performed on n=20 SCD ages 10 – 50 with high risk of recurrent complications (Pain crises, ACS, & Stroke).
- Vascular access mostly peripheral, few central or femoral placed for other reasons not related to RBCX procedure.

Outcomes:

- none of the patients developed complications related to the procedure or to increased blood use.
- It was safe & effective in preventing SCD complications.
- When done automatically, RBCX decreased ferritin levels & reduced iron overload.

Limitations:

- Retrospective, using three platforms of devices & manual exchange

The impact of a regular erythrocytapheresis programme on the acute and chronic complications of sickle cell disease in adults

MAIN POINTS:

- N=13 adult patients (aged 22-63) enrolled in regular erythrocytapheresis for a median duration of 70 months.
- In patients on exchanges every 6 weeks, HbS% was <42% in two and between 47% and 53% in four patients
- No patient experienced stroke or multi-organ crises, evidence of end-organ dysfunction while on RBCX. No patient stopped RBCX during treatment.
- Estimated hospital savings (Aus \$) \$6682 per patient per year (see next slide)

Conclusions:

- RBCX for patients with SCD was an effective, well-tolerated therapy for both acute and chronic complications of SCD, reducing hospital admissions for sickle related acute events.
- Long term RBCX shown benefit in primary and secondary stroke prevention in children with SCD
- Alloimmunization rates were comparable to the literature.
- RBCX was confirmed to be effective at iron control.

Limitations:

- This data is a single centre retrospective study on a small number of patients with no control,
- Vascular access was an issue in a few patients requiring placement of catheters.

MAIN POINTS:

- 10 children (5 treated with manual exchange for 124 procedures; 5 children with automated exchange for 60 procedures)
- Some difficulty with venous access (14 occurrences from 60 procedures) related to impaired blood flow but not requiring cessation or placement of central venous access.
 - Statistically significant ($p < 0.0001$) increase in number of days needed between exchanges. **63 days ARBCX compared to 28 for manual exchange.**
 - Chronic erythrocytapheresis was well tolerated overall. No significant increase in iron overload.

Conclusion:

- The ARBCX procedure is shorter and a nurse can handle two or three patients at the same time.
- Difficulties of venous access are relatively infrequent.
- The cost per session was high, but the lower number of sessions, & hence requiring less patients visits and possibly the long-term impact on the disease of annual hospitalisations must be taken into account.
- Data support the use of RBCX rather than manual exchanges for children with long-term programs of red cell exchange.

Limitations: Small study, 10 children (5 treated with manual exchange for 124 procedures; 5 children with automated exchange for 60 procedures). The fact it is a paediatric study may negate the small numbers.

Main points:

- N=83 patients with SCD in Turkey (age 17 – 49). Underwent 196 automated RBCX between 2003-2006.
- Indications for RBCX were cerebrovascular, priapism, pregnancy, surgery, bone necrosis, & unhealed leg ulcers.
- HbS target <30 % was achieved in most of the procedures.
- Used 20 gauge needle for peripheral access (flow rate 15-60 ml/min). Only 10 procedures required central line catheterization.
- Measured mean transcutaneous oxygen saturation pre & post RBCX: 93% & 97% respectively.
- Measured mean Nitric Oxide (in correlation with plasma nitrite concentration) pre & post: 21 & 19.7 micro mol respectively (improved post RBCX)
- Measured free Hb in plasma (hemolysis) pre & post RBCX: 28.3 & 19.8 mg dl respectively.
- Followed up the patients post RBCX up to 10 months & assessed quality of life related variables besides the clinical outcome.

Conclusion: RBCx prevented VOC & improve QoL.

EXCHANGE BLOOD TRANSFUSION COMPARED WITH SIMPLE TRANSFUSION
FOR FIRST OVERT STROKE IS ASSOCIATED WITH A LOWER RISK OF
SUBSEQUENT STROKE: A RETROSPECTIVE COHORT STUDY OF 137 CHILDREN
WITH SICKLE CELL ANEMIA

Main points:

- Retrospective, Multiple centers (14) and N= 137
- Patients followed at least 5 years for chronic transfusions after stroke.
- Exchange Transfusion (manual & automated) is more effective initial treatment for stroke than ST.
 - possible benefit of RBCX as the preferred transfusion method
 - may prevent recurrent stroke

Limitations :

- *Retrospective – possible differences between the groups (e.g. severity of first stroke)*
- *A cause and effect relationship between the type of treatment and subsequent stroke could not be determined*

Prophylactic red blood cell exchange may be beneficial in the management of sickle cell disease in pregnancy

Suheyli Asma,^{1,2} Ilknur Kozanoglu,^{3,4} Ebru Tarim,⁵ Cagla Sariturk,⁶ Cigdem Gereklioglu,^{1,2} Aydan Akdeniz,⁷ Mutlu Kasar,¹ Nurhilal H. Turgut,¹ Mahmut Yeral,¹ Fatih Kandemir,² Can Boga,¹ and Hakan Ozdogru¹

- Retrospectively evaluated the complications of SCD in 37 pregnant patients who underwent 43 automated RBCX procedures.
- Patients who had undergone prophylactic RBCX (n=24) were compared to a control group (13 patients) who had not undergone RBCX during pregnancy.

Results:

- Four patients in the control group developed Vaso-occlusive events & died.
- Maternal complication were recorded in 21 patients of the study group compared to 7 in the control group.
- Fetal complications were recorded: 1 in control & 1 in study group.

Conclusion: This study demonstrated that prophylactic RBCX during pregnancy is a feasible & safe procedure for prevention of complications & therefore warrants further studies.

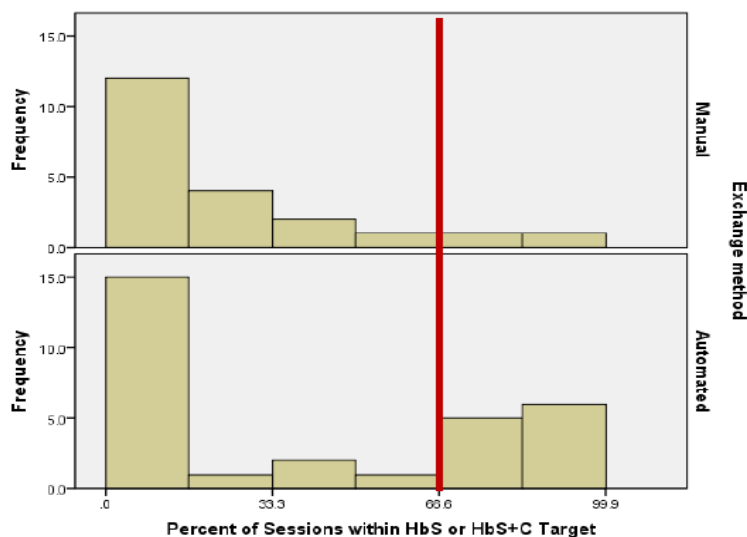
Impact of Long-Term Erythrocytapheresis on Growth and Peak Height Velocity of Children With Sickle Cell Disease

Abhishek Bavle, MBBS,¹ Ashok Raj, MD,^{1,2} Maiying Kong, PhD,³ and Salvatore Bertolone, MD^{1,2}

- They conducted a retrospective chart review of 36 patients with SCD who received long term erythrocytapheresis for on average 5 years. They measured anthropometric data such as weight, height and BMI from the subjects charts to determine if this treatment impacted these measurements.
- Results were compared to measurements prior to erythrocytapheresis.
- Slopes of the curves from height, weight, and BMI all improved with red cell exchange therapy.
- Of the 36 patients in the study, 8 received hydroxyurea prior to being started on erythrocytapheresis. There was no significant improvement on these measures in patients on HU therapy.
- This result is similar to a French paper showing similar information

A comparison of chronic manual and automated red blood cell exchange transfusion in sickle cell disease patients

Ability to Consistently Attain Pre-RBCX HbS/SC Target

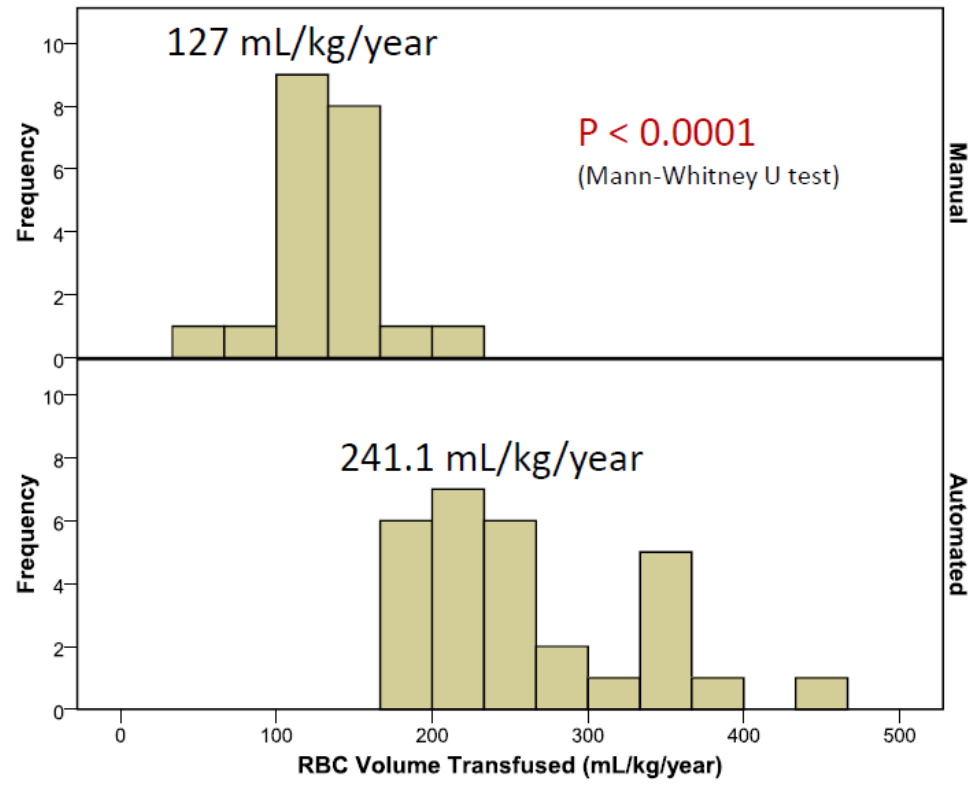


- Patients who had $> 2/3$ of their RBCX sessions within the prescribed pre-RBCX HbS/SC target were considered to be consistently attaining target (based on the STOP2 study entry criteria)

	N (%)	Unadjusted OR (95% CI)	P value
Manual RBCX (N = 21)	2 (10%)	5.50	0.048
Automated RBCX (N = 30)	11 (37%)	(1.072 – 28.22)	

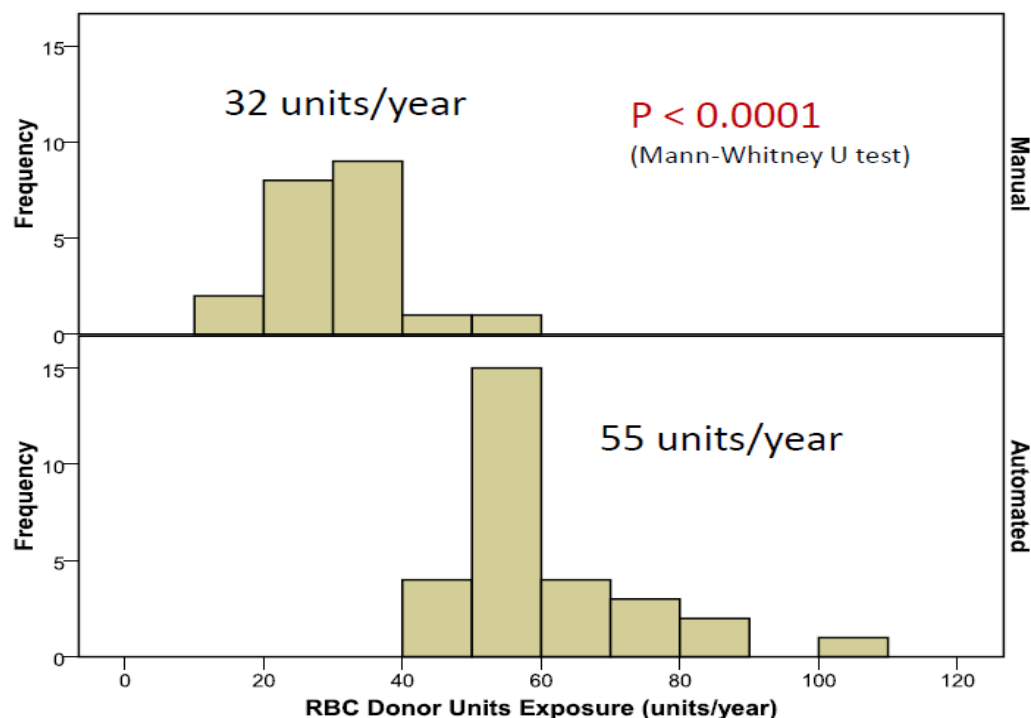
A comparison of chronic manual and automated red blood cell exchange transfusion in sickle cell disease patients

Red Blood Cell Utilization



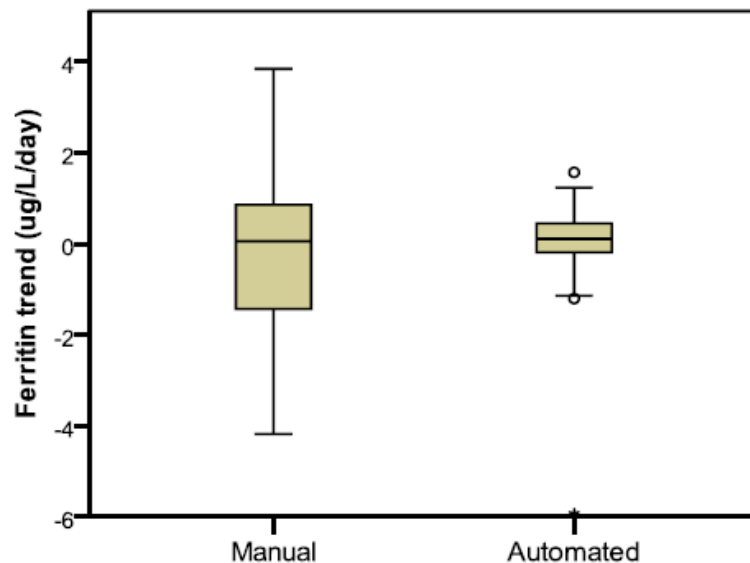
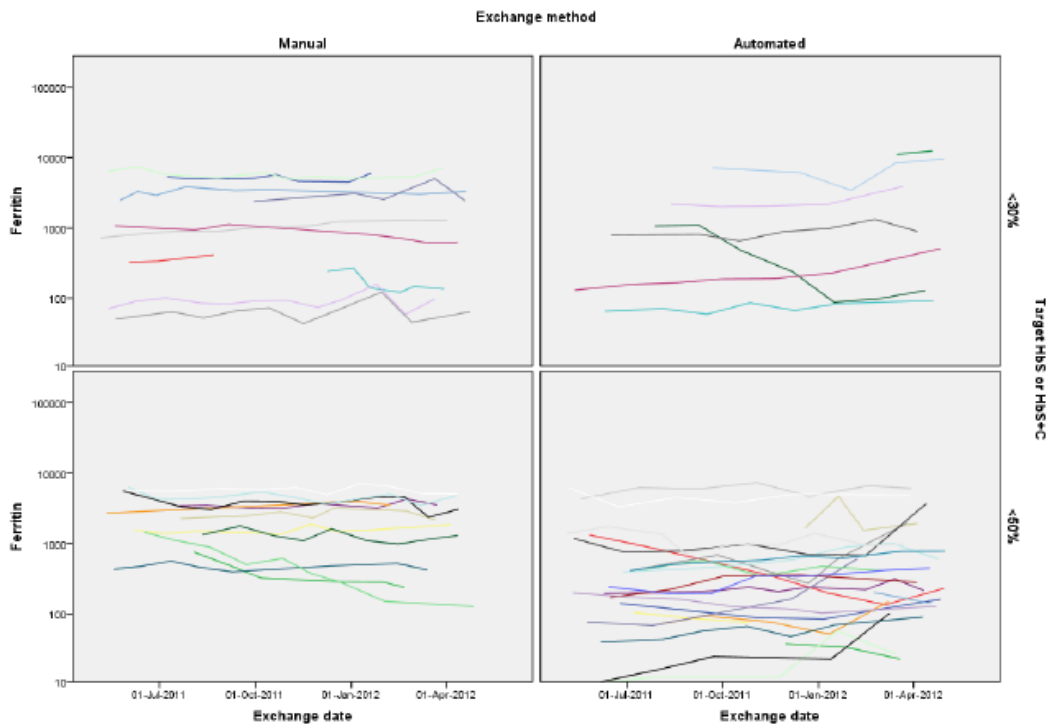
A comparison of chronic manual and automated red blood cell exchange transfusion in sickle cell disease patients

RBC Donor Units Exposure



A comparison of chronic manual and automated red blood cell exchange transfusion in sickle cell disease patients

Iron Balance



A comparison of chronic manual and automated red blood cell exchange transfusion in sickle cell disease patients

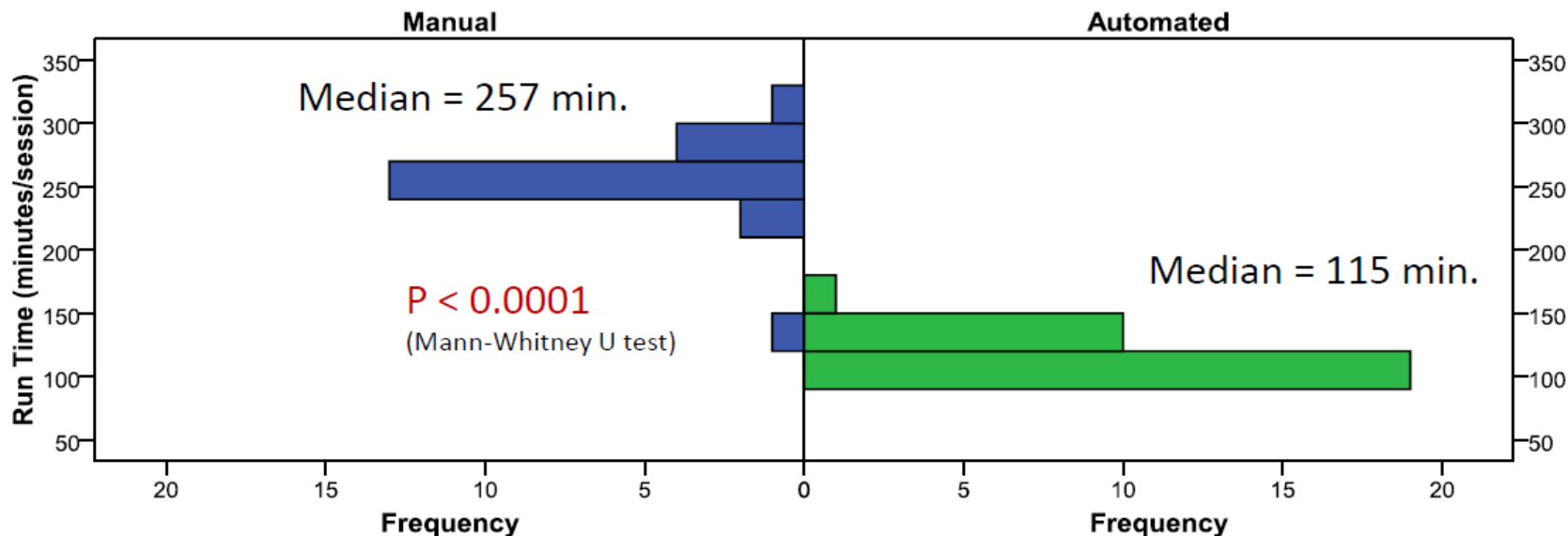
New Antibody Formation

- Automated
 - 1 patient (1 exchange) non-specific antibody
 - 1 patient (1 exchange) inconclusive
- Manual
 - 1 patient (10/10 exchanges) auto anti-e, auto anti-Ce, allo anti-C, allo anti-Kpa, anti-Cw
 - 1 patient (2/11 exchanges) anti-Cw

		Patients with Antibody Formation		P value
		Yes	No	
Method	Manual	2	19	0.7088
	Automated	2	28	

A comparison of chronic manual and automated red blood cell exchange transfusion in sickle cell disease patients

Duration of RBCX Session



A comparison of chronic manual and automated red blood cell exchange transfusion in sickle cell disease patients

Introduction to Depletion RBCX

- In depletion/exchange, a portion of the patient's RBC is first cytapheresed by the apheresis device prior to the exchange phase of the procedure
- Albumin as colloid replacement to maintain intravascular volume and pressure
- The clinical effectiveness of depletion/exchange has not been demonstrated in a systematic manner

A comparison of chronic manual and automated red blood cell exchange transfusion in sickle cell disease patients

Results from a Systematic Comparison of Non-Depletion and Depletion RBCX

- Depletion/exchange reduced RBC usage by 25 mL/kg/year, equivalent to 5 units/60 kg
- Volume of albumin used to maintain euvolemia was 54 mL/kg/year
- No significant difference in pre-RBCX HbS, post-RBCX hematocrit, iron balance, time utilization and adverse events
- Further optimization of the technique by modification of the FCR and minimum Hct may yield higher reduction in RBC usage

Jean-Marie Michot,^{1,2} Françoise Driss,¹ Corinne Guitton,⁴ Julia Moh Klaren,³ François Lefebvre,⁵ Xavier Chamillard,³ Philippe Gallon,³ Erwan Fourn,¹ Alain M. Pela,³ Gérard Tertan,^{1,2} Philippe Le Bras,¹ Christelle Chantalat-Auger,¹ Jean-François Delfraissy,^{1,2} Cécile Goujard,^{1,2} and Olivier Lambotte^{1,2}

MAIN POINTS:

- 188 SCD followed over the period 2006 – 2011, The RBCX and conventional transfusion groups comprised 49 and 139 patients, respectively.
- RBCX enrollment was based on : Severity of SCD, any history of stroke, the degree of iron overload and ability to establish intravenous access. RBCX was used primarily in long-term exchange programs and occasionally before surgery or during pregnancy. RBCX was also used in emergency situations : Acute chest syndrome, severe vasocclusive crisis, stroke and priapism. RBCX each 5 to 6 weeks, received 15 to 25 ml of RBCs/kg
- **All the SCD patients underwent the same pretransfusion procedures, including rhesus and Kell RBC phenotyping and a systematic cross-matching test for detecting any Abs. Cross matching test was performed no more than 72 hours before transfusion**
- **The alloimmunization/RBC unit (RBCU) ratio was lower in the RBCX group than in the conventional transfusion group (1.6 and 11.6 per 1000, respectively)**
- Patients in the RBCX group received 10 times more RBCUs than patients in the conventional transfusion group (206 vs. 19 RBCUs per patient, respectively)
- **RBCX exhibits a good immunohematologic safety profile relative to conventional transfusion in a large SCD mainly adult cohort.**
- **Hemolytic transfusion reactions occurred after conventional transfusion in three cases and after an ECP session in one case, all four patients belonged to the “conventional transfusion” group**

LIMITATIONS :

- Difference between the two groups and the retrospective nature of the study.

A 5-year cost analysis of automated red cell exchange transfusion for the management of recurrent painful crises in adult patients with sickle cell disease

- retrospectively analyzed data on 23 patients intolerant or who fail hydroxycarbamide, chronic transfusions are an alternative. Automated red cell exchange transfusion (ARCET) are more effective in lowering rapidly the HbS level while avoiding iron overload
- Patients have been on a regular programme 1–5 years and found that their utilization of hospital services reduced by 20%, 48%, 58%, 71%, and 79% after 1, 2, 3, 4 and 5 years respectively
- The overall mean annual cost of care per patient was £9702 and £2378 higher than baseline after the 1st and 2nd years of ARCET respectively and then reduced by £5486, £8317, and £14,664 after the 3rd, 4th and 5th year of ARCET respectively indicating that ARCET leads to cost savings to health services in the medium to long term due to reduction in hospital attendance of these patients

Safety, Tolerability, and Outcomes of Regular Automated Red Cell Exchange Transfusion in the Management of Sickle Cell Disease

Dimitris A. Tsitsikas,* Bala Sirigireddy, Ruben Nzouakou, Alexander Calvey, Joanne Quinn, Janine Collins, Funmilayo Orebayo, Natasha Lewis, Sophie Todd, and Roger J. Amos

Haemoglobinopathy Service, Department of Haematology, Homerton University Hospital NHS Foundation Trust, London, United Kingdom

We report here our experience with regular automated red cell exchange transfusion for the management of chronic complications of sickle cell disease in 50 patients in our institution from June 2011 to December 2014. The mean sickle hemoglobin level was 44% and 8.5% pre- and post-transfusion, respectively. Platelets were reduced by a mean 70% during the procedure with a count of less than $50 \times 10^9/l$ in 6% of cases. The alloimmunization rate was 0.065/100 units of red cells with no hemolytic reactions. Patients with no iron overload at baseline showed no evidence of iron accumulation with a mean liver iron concentration of 1.6 mg/g dry tissue and 1.9 mg/g dry tissue at baseline and 36 months, respectively. All six patients with pre-existing iron overload and on chelation therapy, showed a gradual reduction of their liver iron concentration and two patients could discontinue chelation during the follow-up period. Seventy percentage of patients who were on the programme for recurrent painful crises showed a sustained reduction in the number of emergency hospital attendances; the mean number of days in hospital for emergency treatment was 103 in the year prior to commencing ARCET and reduced to 62 (40%) after the first 12 months, 51 (50%) after 24 months, and 35 days (66%) after 36 months. *J. Clin. Apheresis* 00:000–000, 2016. © 2016 Wiley Periodicals, Inc.

Effectiveness of red blood cell exchange, partial manual exchange, and simple transfusion concurrently with iron chelation therapy in reducing iron overload in chronically transfused sickle cell anemia patients

*Ross M. Fasano,^{1,2} Traci Leong,³ Megha Kaushal,⁴ Eyal Sagiv,⁴
Naomi L.C. Luban,^{4,5} and Emily Riehm Meier^{4,5}*

- ❖ Twenty-eight patients were included
- ❖ RBCX does not adversely affect RBC alloimmunization or the ability to maintain the HbS within prescribed pretransfusion HbS target of 30% despite increased reticulocytosis.
- ❖ *“We recommend RBCX plus chelation as an effective method for reducing iron overload, while maintaining HbS at 30% to 35%”*

MEDICAL AFFAIRS



Updates on recent guidelines & recommendations

ASFA 2016 Categories

- Category I
Apheresis is considered primary or standard therapy.
- Category II
There is sufficient evidence to suggest efficacy, usually in an adjunctive role.
- Category III
Insufficient data to determine effectiveness.
Isolated published studies have indicated that it may be of benefit as a “last-ditch” effort.
- Category IV
Controlled trials have not shown benefit.

TABLE II. Grading Recommendations adopted from Guyatt and coworkers [8].

Recommendation	Description	Methodological quality of supporting evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

ASFA 2016 guidelines for RBCx in acute SCD

SICKLE CELL DISEASE, ACUTE

Incidence: 273/100,000 African-Americans(1/375 for Hb SS, 1/835 for Hb SC, 1/1667 for Hb S/ β -thalassemia live births); 89.8/100,000 Hispanics primarily from Caribbean islands	Indication	Procedure	Recommendation	Category
	Acute stroke	RBC exchange	Grade 1C	I
	Acute chest syndrome, severe	RBC exchange	Grade 1C	II
	Priapism	RBC exchange	Grade 2C	III
	Multiorgan failure	RBC exchange	Grade 2C	III
	Splenic/hepatic sequestration; intrahepatic cholestasis	RBC exchange	Grade 2C	III
No. Reported patients: >300 ^a	RCT	CT	CS	CR
Acute stroke	0	1(52)	7(160)	8(10)
Acute chest syndrome	0	2(121)	13(145)	8(8)
Priapism	0	0	1(5)	1(1)
Multisystem organ failure	0	0	3(10)	3(3)
Hepatic sequestration/intrahepatic cholestasis	0	0	1(52)	3(4)
Splenic sequestration	0	0	3(204)	0

^aThe number of reported patients includes patients who received RBC transfusion, manual RBC exchange, or automated RBC exchange.

ASFA 2016 guidelines for RBCx in chronic SCD

<http://apheresisguidelines.com/>

SICKLE CELL DISEASE, NON-ACUTE

Incidence: 273/100,000 African-Americans(1/375 for Hb SS, 1/835 for Hb SC, 1/1667 for Hb S/β-thalassemia live births); 89.8/100,000 Hispanics primarily from Caribbean islands	Indication	Procedure	Recommendation	Category
	Stroke prophylaxis/iron overload prevention	RBC exchange	Grade 1A	I
	Recurrent vaso-occlusive pain crisis	RBC exchange	Grade 2C	III
	Pre- operative management	RBC exchange	Grade 2A	III
	Pregnancy	RBC exchange	Grade 2C	III
No. Reported patients: >300 ^a	RCT	CT	CS	CR
Stroke prophylaxis/iron overload prevention	2(326)	1(36)	20(335)	3(3)
Vaso-occlusive pain crisis	1(130)	1(21)	3(18)	1(1)
Pre-operative management	3(1035)	4(184)	3(957)	0
Pregnancy	0	2(38)	1(5)	0

^aThe number of reported patients includes patients who received RBC transfusion, manual RBC exchange or automated RBC exchange.

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COMMENTARY

WILEY



Red blood CELL exchange: 2015 American Society for Apheresis consensus conference on the management of patients with sickle cell disease

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TABLE 3 Results of electronic polling of speakers and moderators

	Question	Result
1.	Considering the pathophysiology of vaso-occlusive complications, is there high quality evidence to support the reduction of HbS to <30% as acute and/or chronic management of certain complications of SCD?	Yes 6/7 = Strong agreement
2.	What is the quality of evidence in support of transfusion therapy (simple or apheresis-based) for the treatment of patients who present with acute chest syndrome?	High/Moderate 3/5
	A. High/Moderate	Low/Very Low 2/5
	B. Low/Very Low	(2 abstained) = No consensus agreement
3.	If the evidence for transfusion therapy is high or moderate, is the potential benefit of raising the patient's hemoglobin compromised by the decline in 2,3-DPG that occurs during blood bank storage of red cells?	No 7/7 = Unanimous agreement
4.	Does the benefit of transfusion therapy in ACS derive primarily from countering pathophysiology through the reduction in the content of HbS in the patient's blood?	Yes 2/4
		No 2/4 (3 abstained) = No consensus agreement
5.	Does high or moderate quality evidence support the use of red cell exchange as the first line of therapy for patients presenting with ACS?	No 4/5 (2 abstained) = Simple majority agreement
6.	For patients with SCD who present with acute stroke, should red cell exchange, if available, be used as first line therapy, rather than simple transfusion, to achieve rapid reduction of HbS to <30%?	Yes 5/5 (2 abstained) = Simple majority agreement
7.	Chronic red cell exchange can mitigate iron overload that occurs with chronic simple transfusion therapy for complications of SCD such as for primary or secondary stroke prevention and others. Does this justify consideration of red cell exchange as the standard of care for patients requiring chronic transfusion therapy?	Yes 7/7 = Unanimous agreement
8.	Red cell exchange with IHD can increase the interval between procedures, reduce blood utilization and mitigate iron overload in chronically treated patients. Should IHD red cell exchange be considered the preferred therapy for primary or secondary stroke prevention?	No 5/7 = Simple majority agreement
9.	In the treatment of acute chest syndrome, does moderate or high quality evidence support the use of fresh red cells (<7 days of storage)?	No 7/7 = Unanimous agreement
10.	Should red cells for transfusion in SCD be phenotypically matched for Rh and K antigens?	Yes 7/7 = Unanimous agreement
11.	Should red cell units used for patients with SCD be screened for G6PD or for hemoglobinopathies other than sickle cell?	No 7/7 = Unanimous agreement
12.	Is there a role for red cell transfusion or red cell exchange in priapism?	No 6/7 = Majority agreement



Spectra Optia for automatic red blood cell exchange in patients with sickle cell disease

Medical technology guidance

Published: 2 March 2016

[nice.org.uk/guidance/mtg28](https://www.nice.org.uk/guidance/mtg28)

1 Recommendations

- 1.1 The case for adopting Spectra Optia for automated red blood cell exchange in patients with sickle cell disease is supported by the evidence. Spectra Optia is faster to use and needs to be done less often than manual red blood cell exchange.
- 1.2 Spectra Optia should be considered for automated red blood cell exchange in patients with sickle cell disease who need regular transfusion.
- 1.3 NICE recommends collaborative data collection to generate further clinical evidence on some outcomes of treatment with Spectra Optia. In particular, there is a need for long-term data on how automated and manual exchange affect iron overload status and the subsequent need for chelation therapy.
- 1.4 Based on current evidence and expert advice on the anticipated benefits of the technology when used in patients with iron overload, cost modelling shows that in most cases using Spectra Optia is cost saving compared with manual red blood cell exchange or top-up transfusion. The savings depend on the iron overload status of the patient, and are more likely to be achieved if devices already owned by the NHS can be used to treat sickle cell disease. The estimated cost saving for adopting Spectra Optia is £18,100 per patient per year, which has the potential to save the NHS in England £12.9 million each year.

“Do Not Do Recommendations” by NICE

Top-up transfusion is not generally suitable as a long-term regime for sickle cell disease because it is iron positive.

Do Not Do Recommendation Details

Recommendation:

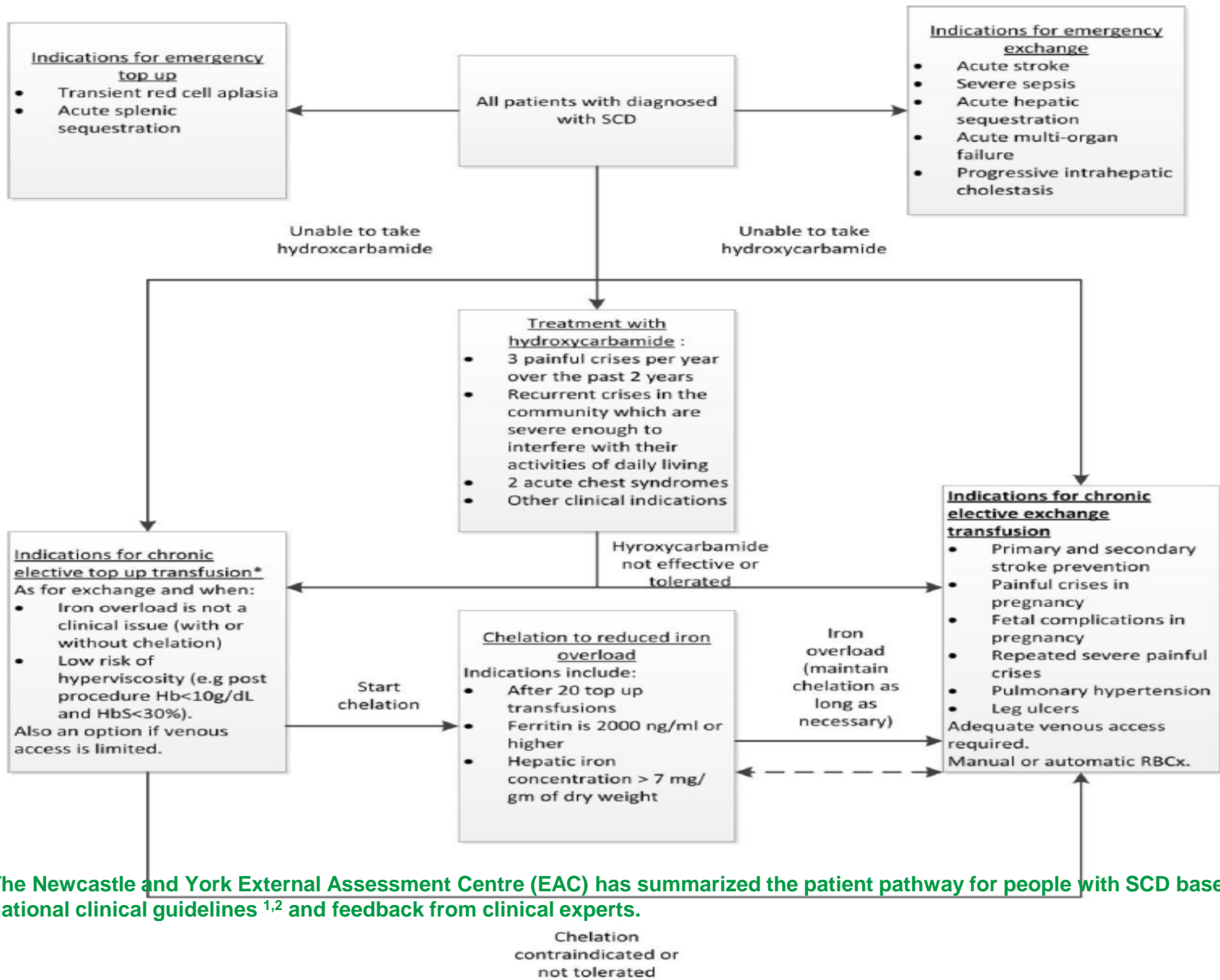
Top-up transfusion is not generally suitable as a long-term regime for sickle cell disease because it is iron positive.

Interventions:

Top-up transfusion

www.nice.org.uk/donotdo/top-up-transfusion-is-not-generally-suitable-as-a-long-term-regime-for-sickle-cell-disease-because-it-is-iron-positive

Figure 1: Patient pathway for people with Sick Cell Disease



The Newcastle and York External Assessment Centre (EAC) has summarized the patient pathway for people with SCD based on the UK national clinical guidelines^{1,2} and feedback from clinical experts.



Round table discussion:

- What are the common challenges in managing SCD patients?
- How blood is sourced, screened, and phenotyped?
- What about patients access to therapy, logistics, and education about SCD.
- Collaboration between service providers & clinical hematology network
- What about national guidelines or patients treatment pathway.
- How automated RBCx perceived by patients & their family perspective but also by referring physicians.

WORKSHOP #1: KEY CHALLENGES

- Vascular Access (***)
 - SN access?
 - Poor venous access
 - Adults / Peds
 - Custom Prime
- Physician / Nurse Awareness and Education about SCD treatment options (***)
- Availability of (matched) blood (***)
- Extended phenotyping (to prevent allo-immunization)
- Finding Resources / Skilled – Trained Staff (**)
- Patient Support and Education
- Blood Safety
- Switching from Manual to Automatic